## REMARKS

Claims 7-12, 14-18, 20-28, and 30-31 are pending herein. By this Amendment, Claims 19 and 29 are canceled; Claims 17-18 and 22 are amended; and new Claims 30-31 are added. Support for the claim amendments and new claims is found in the specification at, *inter alia*, paragraphs [0013], [0015], [0051] and the Abstract. No new matter is added by this Amendment.

### I. REJOINDER

Applicants respectfully request rejoinder of withdrawn Claims 7-12, 14, and 17 upon allowance of the pending claims.

### II. THE PRESENT INVENTION

There appears to be a fundamental misconception about Applicant's invention. The claimed invention is directed to a field-tested method for assessing the practical or acceptable ecological risk to mammals in a terrestrial system. *See* paragraphs [0012] and [0064] of the present specification. The claimed methods utilize a reproductive endpoint and sperm parameter benchmarks for rodents to make the assessment as to whether ecological risk for other terrestrial site mammals is present or not. The present methods therefore serve as a "red flag" for ecological risk for mammals at a contaminated site. Contrary to the Examiner's position, it is not the objective or purpose of Applicant's claimed methods to scale up exposure-related data for rodents to obtain numerical values (degrees of risk) for other site mammals.

According to the present invention, if rodents at a contaminated site are not experiencing impaired reproductive capability, it is concluded that other terrestrial site mammals are also not experiencing compromised reproductive success. *See* paragraph [0051]. Alternatively, if rodents at a contaminated site are experiencing compromised reproductive success, by implication it is concluded that other "site terrestrial ecological receptors have the potential to be experiencing similar reduce reproductive success." *See* paragraph [0013]. Given this understanding of the claimed

methods, one of ordinary skill in the art would have been able to practice the invention without undue experimentation.

III. REJECTION UNDER 35 U.S.C. 112, FIRST PARAGRAPH

Claims 15-16 and 18-29 were rejected under 35 U.S.C. 112, first paragraph, as assertedly being non-enabled. This rejection is respectfully traversed.

A. Enablement Analysis

In view of the correct understanding of Applicant's invention, the analysis of the *In re Wands* factors to determine enablement is as follows:

(1) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

As noted, the claimed methods have a specific purpose to make the assessment as to whether detrimental effects for other terrestrial site mammals are present or not. It is not the purpose of the claimed methods to scale up exposure-related data for rodents to obtain numerical values for other mammals. Thus, a great deal of experimentation is unnecessary.

(2) The amount of direction provided by the inventor.

The purpose of the claimed invention is not to "derive data" for other mammals. Applicant clearly lays out the methodology for assessing ecological risk based on rodent sperm analysis. *See* paragraphs [0043]-[0051].

(3) The existence of working examples.

The specification provides working examples of determining whether the comparison between the sperm count, sperm motility, and sperm morphology of rodents from a contaminated site and of rodents from an animal reference site exceeds sperm parameter benchmarks for sperm count, sperm motility, and sperm morphology, thereby indicating if the rodents from the contaminated site have compromised reproductive success. *See* paragraphs [0052]-[0068].

(4) The nature of the invention.

Contrary to the Examiner's assertion, the invention is not directed to assessing how mammals "will react to a contaminated site" or to "environmental changes." As noted, the claimed methods make a determination about whether an ecological risk to mammals at the contaminated site is present or not.

(5) The state of the prior art.

The prior art as discussed below clearly supports using rodent models and their reproductive endpoint to assess ecological risk for other species.

(6) The relative skill of those in the art.

The level of one of ordinary skill in the art would be an individual having a bachelor's degree in biology.

(7) The level of predictability in the art.

Again, the invention is not directed to "extrapolating the results of one mammal to another different mammal" in terms of scaling rodent data. Thus, the unpredictability of environmental effects is not pertinent, especially in view of the standard practice of using rodent models to assess ecological risk for other species.

(8) The breadth of the claims.

The claims must be considered in their entirety. The claims are not broadly directed to assessing the ecological risk to animals. Rather, the claimed methods are directed to using rodent sperm parameter benchmarks to make an assessment about practical ecological risk to other site mammals.

B. Additional Analysis of Record

The Examiner's additional comments regarding non-enablement have been addressed in (1) the Combined Declaration Under 37 C.F.R. 1.131 and 1.132 filed on May 6, 2008 and (2) the Summary of Examiner Interview and Supplemental Remarks filed on June 16, 2008, and are re-emphasized as follows.

1. Working Article

The Examiner argues that Working, *Male Reproductive Toxicology: Comparison of the Human to Animal Models*, Environmental Health Perspectives, Vol. 77, 37-44 (1988) discloses that the "fertility of animal models may be an insensitive indicator of human reproductive risk" (page 38, right hand column). When considering the Working article, it is axiomatic that the article must be considered as a whole.

In its entirety, Working supports Applicant's methodology. Working acknowledges that common animal models may show a large decrease in fertility but still remain maximally fertile, unlike the human male (page 38). In particular, Working states that animal models may experience a decrease of 60-80% "in parameter X", but still remain maximally fertile, which is entirely in accord with the analysis in paragraphs [0048]-[0049] of the specification. Working's statement that "fertility of animal models may be an insensitive indicator of human reproductive risk" is due to the fact that Working does not recognize or appreciate Applicant's use of sperm parameter benchmarks or thresholds-for-effect.

Further, Working proceeds to conduct comparisons of sperm counts, sperm motility, and sperm morphology in humans and animal models. As indicated on page 5 of the Combined Declaration Under 37 C.F.R. 1.131 and 1.132, Working states that no single reproductive end point in any laboratory animal model can serve as an accurate indicator of reproductive risk in the human male (page 43, right hand column). Working also indicates that using computer-assisted videomicrographic methods provide value in risk assessment procedures (Abstract). Thus, Working validates the use of animal models and sperm parameters to make assessments about reproductive risk.

Working is directed to evaluating a specific reproductive risk from individual toxicants, unlike the present invention which is directed to ecological risk. Nevertheless, the Examiner's contention that Working renders that claimed methods for assessing ecological risk non-enabled is incorrect.

2. The Claimed Methods Do Not Require Numerical Adjustments of Any Data

The Examiner argues that, because hazard quotients must be adjusted for different mammals, the claimed methods would appear to require the same adjustments to extrapolate the data of mice to other mammals (Office Action at pages 5-6). The Examiner also asserts that because of other mammals' lack of sensitivity to the environment, other mammals would not be as likely to develop the same effects as mice (Office Action are page 6).

As noted in Section II above, the purpose of the claimed methods for assessing ecological risk is not to scale data obtained from mice to obtain numerical exposure-related values or degrees of risk for other mammals. Rather, the claimed methods act as an assessment about the presence or absence of practical risk to terrestrial site mammals based upon the presence of compromised reproductive success for rodents at a contaminated site. Independent Claims 18 and 22 have been amended to make this distinction more explicit.

As discussed in the Summary of Examiner Interview and Supplemental Remarks on pages 3-4, when using a mouse or a rat no-effect dose or effect-level dose as the denominator of the HQ, it is routine to assert that other mammals are capable of, and do, develop the same toxicological effects as test rodents. Adjustments with regard to body weight, home range, and ingestion rate may be made; however, such adjustments only affect the magnitude of the HQ and have nothing to do with the assumption that site mammals will develop the same effect as the test rodents.

Other than for rodents, no one knows how much exposure is required to trigger compromised sperm parameters in any species. Thus, for the claimed methods in which rodent sperm parameter benchmarks are exceeded, it is correct to assume that the requisite exposures to trigger sperm and other reproductive effects in site mammals -- which by definition are less fertile that rodents -- may be occurring.

3. The Sample et al. Reference and EPA Guidelines

The Examiner asserts that the EPA Guidelines are only addressed toward "the agent or xenobiotic itself". Thus, while an agent may be toxic to both humans and mice, humans may not be exposed to the agent if the agent is located in an environment only accessible to mice (Office Action art page 6).

First, ecological risk assessment for mammals using rodents is standard. Sample et al., *Toxicological Benchmarks for Wildlife: 1996 Revision* was discussed on page 3 of the Combined Declaration Under 37 C.F.R. 1.131 and 1.132. Attached hereto is a Declaration Under 37 C.F.R. 1.132 from Dr. Sample himself stating that the toxicity to rodents is, in fact, "used a surrogate for effects to other mammals". Dr. Sample also notes that 85% of the mammalian toxicity studies in that article had either mice or rats as the laboratory test species.

Thus, in laboratory-based ecological risk assessment, the toxicological endpoint that occurs in the rodent is summarily assumed to also occur in the mammal species being evaluated. A copy of Sample et al. was submitted with an Information Disclosure Statement filed on November 6, 2007. Applicant has not received a copy of this IDS initialed by the Examiner. Applicant respectfully requests that the next Action from the PTO include an initialed copy of this IDS.

Second, the EPA Guidelines support applying rodent reproduction data to human assessment. Thus, in view of Sample et al. and the EPA Guidelines, using rodent reproduction data in ecological risk assessment of mammals including humans is warranted.

## V. CONCLUSION

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited.

If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

Respectfully submitted,

/Warren Zitlau/

Warren A. Zitlau, Esq.
Reg. No. 39,085

CAHN & SAMUELS, LLP
1100 17th Street, N.W., Suite 401
Washington, D.C. 20036
Telephone: (202) 331-8777
Facsimile: (202) 331-3838

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